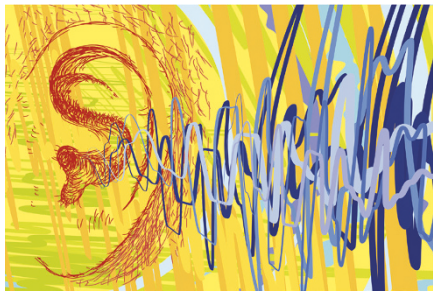
Reversing neurodegenerative hearing loss

Exposure to loud noises can damage the synapses connecting nerves and hair cells in the cochlea of the ear, causing noise-induced hearing loss that can be permanent. Effective strategies to prevent or reverse this damage and the associated hearing loss are lacking. The coenzyme nicotinamide adenine dinucleotide (NAD^+) can protect neurons from damage *in vitro*, but its activity *in vivo* has proven difficult to test because the compound degrades quickly in serum and is not readily taken up by cells. A group of researchers found a way around that limitation by testing the effects of the NAD^+ precursor nicotinamide riboside (NR), which enters cells much more easily than does NAD^+. Administration of NR to C57BL/6 mice, which are highly susceptible to noise-induced hearing loss, boosted levels of NAD^+ in the cochlea and prevented damage to cochlear synapses after noise exposure (*Cell Metab.* **20**, 1059–1068; 2014). As a result, the NR-treated mice did not develop short- or long-term noise-induced hearing loss. Notably, they were protected



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whether NR was administered before or after noise exposure. Administration of NR prior to noise exposure similarly protected mice of two other strains from synaptic damage and resulting hearing loss, indicating that the effects persisted across genetic backgrounds.

The researchers investigated the biochemical mechanism underlying the protective effects of NR and found that they were mediated by the NAD^+-dependent mitochondrial protein sirtuin 3 (SIRT3). Transgenic mice overexpressing SIRT3 were resistant to noise-induced hearing loss even in the absence of NR administration, and knockout mice lacking SIRT3 derived no protective benefit from NR administration.

Kevin Brown (University of North Carolina School of Medicine, Chapel Hill) led the study while he was at Weill Medical College (Cornell University, New York, NY). He explained the importance of the findings in a press release: "One of the major limitations in managing disorders of the inner ear, including hearing loss, is there are a very limited number of treatment options. This discovery identifies a unique pathway and a potential drug therapy to treat noise-induced hearing loss." NR administration may have other clinical applications as well. In a commentary published alongside the article in *Cell Metabolism*, Charles Brenner (Carver College of Medicine, University of Iowa, Iowa City), who was not associated with the study, wrote, "future experiments are expected to clarify…whether NR can be used to prevent or treat additional neurodegenerative diseases and conditions."

Monica Harrington

MANIPULATING MITOCHONDRIA TO TREAT DISEASE

Parkinson's disease (PD) is a neurological disorder caused by the degeneration of dopamine neurons in the brain. Current therapies for this debilitating disease are far from adequate, but a new study suggests that targeting mitochondrial dysfunction in dopamine neurons may be a promising approach to treatment.

Mitochondrial dysfunction has been reported in both familial and sporadic PD. Genetic mutations of proteins that adversely affect mitochondrial function, including PTEN-induced putative kinase-1 (PINK1), have been linked to PD. Mitochondrial dysfunction is also thought to underlie PD induced by synthetic meperidine contaminated with the drug 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).

To study the relationship between mitochondrial dysfunction and PD, scientists at the University of Rochester (NY) led by Kim Tieu used two mouse models: one to model genetic PD and one to model environmentally induced PD. In the first model, the gene encoding PINK1 was deleted in the mice. In the second model, mice were administered MPTP. Both groups of mice showed the deficits in striatal dopamine release characteristic of PD, as well as impairments in mitochondrial respiratory function (*Nat. Commun.* **5**, 5244; 2014).

The processes of mitochondrial fission and fusion have an important role in the function of these organelles, because they influence their shape, size, number and location within cells. Mitochondrial fission produces multiple smaller mitochondria, a process that requires the recruitment of the GTPase dynamin-related protein 1 (Drp1) from the cytosol to the outer mitochondrial membrane. In previous studies in PD cell culture models, blocking Drp1 function mitigated mitochondrial dysfunction and neurotoxicity; however, this approach had yet to be tested in animal models.

Using their two PD mouse models, Tieu's team delivered mutated Drp1 to dopamine neurons using an adenovirus in order to inhibit mitochondrial fission in these mice. In the mice lacking PINK1, inhibition of Drp1 attenuated the deficits in mitochondrial respiration and restored pre-existing striatal dopamine release. Similarly, in the mice that had been given MPTP, Drp1 inhibition prevented loss of dopamine neurons.

Said Tieu in a press release, "Our findings show exciting potential for an effective treatment for PD and pave the way for future in-depth studies in this field." He added, "It's worth noting that other researchers are also targeting this mitochondrial fission/fusion pathway as potential treatments for other neurological diseases such as Alzheimer's disease, Huntington's disease and Amyotrophic Lateral Sclerosis."

Kara Rosania